REMARKS

Claims 1-15 are pending. Claims 8-9 are withdrawn from consideration. All pending, non-withdrawn claims were rejected in the Final Rejection.

Applicants filed a response to the Final Rejection on December 22, 1004. Applicants received an Advisory Action dated as mailed March 15, 2005. In the Advisory Action, the Office stated that none of the amendments submitted in the response filed December 22, 2004 would be entered upon appeal, but observed that the reply overcame the rejections under 35 U.S.C. § 112, second paragraph.

In the prior non-entered response, Applicants again requested clarification regarding claims 8 and 9. Applicants maintain that claims 8 and 9 should not have been withdrawn. Claims 8 and 9 are not directed to the other species delineated. Indeed, claim 8 depends from claim 7; claim 9 depends from claim 8. In the Advisory Action, the Office advised that claims 8 and 9 would not be rejoined as no generic claim was found allowable. With all due respect, the issue is that these claims should not have been withdrawn initially.

Applicants again note with appreciation the Examiner's acknowledgement that claim 3 was dependent only from claim 1, as well as the removal of all previous rejections and objections. Applicants submit the following arguments in response to the new rejections levied against the claims in the Final Rejection. Because the Office said the prior amendments and, presumably, the prior response were not entered, Applicants

are resubmitting their arguments regarding the rejections levied in the Final Rejection, with some further clarifications to address issues raised in the Advisory Action. See MPEP § 714.20 regarding the general rule against entry of an amendment in part.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-7 and 10-15 were rejected in the Final Rejection under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office took issue with the recitation "increasing the circulating half-life of said fragment." The Office's position was that one does not know what the structural features of the molecules are that do not have an increased half-life. Applicants respectfully submit that it is clear from the claims that the structural features of the molecules that do not have an increased half life are that they do not have the polymer molecules attached. The complete claim recitation is "at least one **polymer** molecule **effective** for increasing the circulating half-life of said fragment." Since, as recited in the claims, the polymer molecule is what is responsible for increasing the circulating half-life of the fragment, the structural feature of the molecules that do not have an increased half-life are those that do **not** have the polymer.

Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-7 and 10-15 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office alleged that the recitation "effective for increasing the circulating half-life of said

fragment" was new matter. This rejection was maintained in the Advisory Action. The Office alleges that the original disclosure taught that the increased half-life was in comparison to the divalent antibody with the polymer randomly attached whereas the claims now read that the increased half-life is in comparison to the divalent antibody sans the polymer. Applicants again traverse this rejection.

With all due respect, the Office's allegation continues to exhibit a misapprehension of the invention. It is not the "randomness" of the attachment of the polymer that increases the circulating half-life, but the attachment of the polymer itself (see, for example, page 2, lines 1-14, of the application as filed). Although the Office considers the passage cited to be a general review of the state of the art, it is clearly linked to Applicant's invention by the discussion on page 3, lines 25-33, of the application as filed wherein it is stated that the invention comprises a divalent antibody fragment comprising a polymer molecule in covalent linkage. The randomness of attachment, rather, can affect the affinity, avidity, or specificity of the antibody (see page 3, lines 1-12, of the application as filed.) Applicants' invention strikes a balance between achieving a desired increase in circulating half-life through the addition of a polymer and the undesired decrease in binding affinity/avidity/specificity that can accompany the same.

Applicants also cited Table 2 and Figure 5 as support for the amendment. The Office stated that it was unclear what the abbreviations "DFM" and "DFM-PEG" mean,

alleging that the text does not adequately explain them. At page 15, line 30, of the application as filed, DFM-PEG is described to be an antibody fragment in which two Fab' fragments are cross-linked with a PEGylated dimaleimide bridge. On page 20, line 25, of the application as filed, DFM is described as diFab' cross-linked with BMH. BMH is described to be bismaleimidohexane on page 16, line 5, of the application as filed.

The Office's comments in the Final Rejection about the Applicants' examples being intended to be comparisons between random and non-random attachment is not accurate. Indeed, the results reporting pharmokinetic data do not specify whether the PEG is random or non-random. See, for example, the results reported in Tables 2 and 6. The results reporting antigen binding, however, do specify how the PEG is attached. See, for example, Tables 1 , 3, 4, and 5, of the application as filed. Regardless, Applicants note that claim 1, as filed, specifies that the polymer molecule is part of the non-disulphide bridge between two cysteine residues. This location is not random.

Applicants respectfully request that this rejection be withdrawn.

Claims 1-7 and 10-15 were rejected as allegedly failing to comply with the written description requirement in the Final Rejection because, in the Office's view, Applicants did not possess the genus of divalent antibody fragments having a covalently linked polymer effective for increasing circulating half-life of the fragment. The Office alleged that Applicants' disclosure attempts to encompass anything and everything in terms of the nature of the inter-chain bridge and in terms of the polymer covalently

attached thereto. The Office stated that it was not clear whether the purpose of covalently linking the polymer to the inter-chain bridge was for improving affinity/avidity/specificity or pharmokinetic properties or both. This rejection was repeated in the Advisory Action. Applicants traverse this rejection.

First, the claims do not recite that the polymer is attached to simply any inter-chain bridge anywhere on the fragment. The inter-chain bridge is a non-disulphide bridge between two cysteine residues located outside of the variable region domain of each chain (*see* claim 1). Second, Applicants respectfully submit that even a cursory review of the specification answers the question posed by the Office – attaching the polymer to an inter-chain bridge between two cysteine residues outside the variable region domain increases circulating half-life without negatively impacting affinity/avidity/specificity (*see*, for example, the Abstract, page 3, lines 17-23, and Table 1 of the application as filed). The polymer increases circulating half-life; the attachment location, i.e., outside the variable region domain, decreases the potential negative impact on binding, i.e., lowered affinity/avidity/specificity, that the polymer might otherwise have.

The Office is further of the view that Applicants do not define a line of demarcation between those polymers that do and those that do not increase the circulating half-life. The Office is, respectfully, misapprehending the invention. The invention is not simply to increase circulating half-life of the antibody fragments, but to increase

circulating half-life of the antibody fragments **with** a minimal effect on binding. Further, in some instances, i.e., when penetration of tissue is desired, a large polymer is not desirous (*see* page 6, line 39, through page 7, line 3, or the application as filed). Clearly, for applications in which tissue penetration is desired, even a minimal increase in circulating half-life, such as that achieved with a smaller polymer, is beneficial. The Office stated, in the Final Rejection, that Applicants have only exemplified that PEG of 10K, 20K, and 40K increases circulating half-life. This statement, however, is not correct. See, for example, Table 4 and Figure 7 of the application as filed. The Office is attempting to unduly limit Applicants to a particular size of polymer based upon a continued misapprehension of the invention.

The Office also argued that Applicants did not disclose what other properties (besides size) of the polymer are important in contributing to an increase in circulating half-life. The Office argued that Applicants are claiming a subgenus of conjugates in terms of a functional property not linked to a common structure and that this does not meet the written description requirement. This observation was repeated in the Advisory Action. The Office cited UC v. Eli Lilly, 43 USPQ2d 1398, in support, in the Final Rejection. Eli Lilly, however, is distinguishable. The Court in Eli Lilly found that a definition by function alone did not suffice to disclose a specific cDNA because it is only an indication of what the cDNA does rather than what it is. *Regents of the University of*

California v. Eli Lilly, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). Applicants are not claiming cDNA.

Indeed, Applicants are not even claiming a specific polymer. Again, it is not the type of polymer that is important, but that there is **a** polymer. This proposition is clear from the application as filed. See, for example, the discussion on page 6, lines 8-27, of the application as filed. A list of potential polymers is therein provided. Also, see Tables 2 and 6, of the application as filed.

Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102(e)

Claims 1-7 and 10-13, and 15 were rejected as allegedly entirely anticipated by Gonzales et al (6,025,158) in the Final Rejection. This rejection was maintained in the Advisory Action. Applicants respectfully traverse this rejection. A careful review of Gonzales et al reveals that it does not anticipate Applicants' invention.

Claim 1 has been amended herein to clarify that the polymer molecule is part of a non-disulphide interchain bridge between two cysteine residues. Support for this recitation can be found, *inter alia*, on page 7, lines 5-9, of the application as filed. Gonzales et al does not disclose a divalent antibody fragment as claimed.

All specific discussions of divalent antibody fragments, specify that the polymer is attached to a cysteine and, further, that an interchain bridge is **avoided entirely** by substituting one of the cysteine residues that normally would form the bridge with a

serine. See, for example, the discussion at column 23, line 17, through column 25, line 44, and the discussion at column 31, line 55, through column 34, line 28, of Gonzales et al. See also the description of Example U at col. 123, lines 15-37. Preparation of a pegylated $F(ab')_2$ is described. The PEG is attached to lysines using N-hydroxysuccinamide chemistry. Example W also describes the preparation of PEG-modified $F(ab')_2$ using the succinimidyl chemical coupling method, i.e., attachment to lysines (see col. 126, line 55, through col. 127, line 60).

Contrastingly, the general passages relied upon by the Office as describing a divalent antibody fragment (i.e., col. 35, lines 40-57, and col. 41, lines 41-62) **do not specify** where on the antibody fragments the polymer is to be attached. The attachment location cannot be read into the reference. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131, citing, *inter alia*, *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Nor can an argument be made that the claimed invention is inherently disclosed.

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or

possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'

MPEP 2112, IV, citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

The other passages cited by the Office, specifying that attachment to the hinge, are not helpful. These passages do not specify where in the hinge the polymer is to be attached.

In view of the foregoing, Gonzales et al clearly fails to anticipate claim 1. As claims 2-7 and 10-13 and 15 ultimately depend from claim 1, Gonzales et al similarly fails to anticipate these claims as well. Nonetheless, the assertions of the Office regarding claims 4 and 5 will be addressed.

The Office asserted that the embodiments in which Fab' or Fab'-SH fragments are employed is "consistent with" claim 4. As is clear from the citation to MPEP 2131 above, "consistent with" is not the standard for determining anticipation. Furthermore, the claims recite "divalent antibody fragments." Fab' and Fab'-SH are monovalent.

Regarding claim 5, none of the passages cited by the Office are referring to divalent antibody fragments. Accordingly, none of the passages anticipates Applicants' claims.

Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 1 and 13-14 were rejected as allegedly unpatentable over Gonzales et al in view of Barbanti et al (5,436,154). This rejection was maintained in the Advisory Action. Applicants traverse this rejection.

The Office stated that Gonzales et al had been noted for "generically teaching the coupling/bridging of Fab, Fab', or Fab'-SH antibody fragments of generic binding specificity, or more particularly of IL-8 binding specificity, to a polymer to extend circulating half-life" (Office Action, page 7). Again, the claims recite divalent antibody fragments. None of the fragments noted by the Office are divalent. Regardless, for the reasons discussed above, discussion incorporated herein, the discussions in Gonzales et al of divalent antibody fragments did not disclose Applicants' claimed invention, nor do they suggest it.

Applicants claims recite that the polymer is part of the non-disulphide interchain bridge linking the sulphur atoms of two cysteine residues. As discussed above, discussion incorporated herein, Gonzales et al actually teaches away from a non-disulphide inter-chain bridge between two cysteine residues by discussing the purposeful avoidance of the same by changing of one of the cysteine residues to serine. Barbanti et al does not overcome this deficiency. As noted by the Examiner, Barbanti et al describes antibodies to TNF-alpha, not antibody fragments conjugated to a polymer for increasing circulating half-life.

Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the above-identified application is now in condition for allowance and request early notification of the same.

Respectfully submitted,

Doreen Yatko Trujillo

Doreen Yatko Trujillo
Registration No. 35,719

Date: April 25, 2005

COZEN O'CONNOR, P.C.
1900 Market Street, 6th Floor
Philadelphia, PA 19103-3508
Telephone: (215) 665-5593
Facsimile: (215) 701-2005